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Remarks

The Claimed Invention

Claim 27 is drawn to a peptide composition comprising a peptide having a defined sequence, wherein the peptide is up to about 40 amino acids and is present either in free form or bound to a carrier molecule. The claim has been amended to delete SEQ ID NO:24.

Priority Claim to U.S. Patent No. 6,232,522

U.S. patent No. 6,232,522 issued on U.S.S.N. 160,604 filed November 30, 1993, and is assigned to Oklahoma Medical Research Foundation, Oklahoma City, OK.

This application was filed by John B. Harley and Judith A. James on January 13, 1997, claiming priority to U.S.S.N. 160,604 filed November 30, 1993, and is assigned to the Oklahoma Medical Research Foundation.

35 U.S.C. 102(e) refers to prior art as "a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent." 35 U.S.C. 120 provides "An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which ***is filed by an inventor or inventors named by the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application***. . . ." (emphasis added)

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This application is commonly assigned with U.S. Patent No. 6,232,522, and shares two common inventors. It was filed prior to issuance of U.S. Patent No. 6,232,522, on May 15, 2001, with a claim to priority (see Declaration and page 1, lines 5-12 of the application). Harley discloses at least one peptide in common, SEQ ID NO:1, PPPGMRPP. Even though this peptide was derived from the autoantigen, RO/SSA, the peptide which is claimed by claim 27 and the peptide which applicants disclosed in their earlier application are the same. Use of this peptide for the same purpose, to induce tolerance and as a diagnostic reagent, is also disclosed (col. 10, line 39, to col. 13, line 4). Accordingly, the claims are entitled to benefit of the earlier filed application.

The examiner's rejection is inconsistent. On the one hand, the examiner says that the claim is not entitled to priority to U.S.S.N. 160,604; on the other hand, the examiner says that the claim is anticipated by U.S.S.N. 160,604. One cannot have both situations. In the office action mailed July 18, 2002, the examiner denied priority based on the argument that the priority application disclosed octamers while SEQ ID NO. 24 is a nonomer. The examiner has not responded to applicants' explanation of why this is not correct, nor has she identified any basis on which applicants have failed to comply with 35 U.S.C. 120.

Rejections Under 35 U.S.C. § 102

Claim 27 was rejected under 35 U.S.C. §102(b) over PCT WO 94/06912 to Middeldorp or under 35 U.S.C. 102(e) over U.S. patent No. 5,965,353. Claims 27-29 were rejected under 35

U.S.C. 102(e) as anticipated by U.S. patent No. 6,232,522 to Harley, et al. These rejections are respectfully traversed.

Middledorp

The basis for the examiner's rejection over Middledorp PCT is that SEQ ID NO:4 of Middledorp PCT is the same as SEQ ID NO:24. This is not correct. The Middeldorp PCT application does not disclose SEQ ID NO:24. SEQ ID NO:6 of the Middeldorp **patent** appears to correspond to SEQ ID NO:24, even though the description in the text is inconsistent.

To moot this issue, Claim 27 no longer includes SEQ ID NO:24, and cannot therefore be anticipated by either Middeldorp.

Harley

Harley is discussed above. Harley is not available as prior art to this application.

Rejections Under 35 U.S.C. § 103

Claims 28 and 29 have apparently been rejected under 35 U.S.C. 103, although the office action merely refers to earlier unidentified office actions. This is clearly improper. To the extent the examiner was referring to the office action mailed July 18, 2002, one still cannot ascertain what the basis of this rejection is, although there is some discussion of "Middeldorp". This is also improper. Referring to the previous office action mailed January 31, 2001, claims 28 and 29 were rejected under §103 over U.S. patent No. 5,965,353 to Middeldorp. This rejection is respectfully traversed.

Claims 28 and 29 are drawn to the use of peptides reactive with autoantibodies to induce tolerance. Claim 28 has been amended to clarify that the peptide is administered to a patient with autoimmune disease in an amount effective to induce tolerance to EBV-induced autoimmune responses characterized by the presence of autoantibodies. Support for these amendments is found in the application at page 20, lines 8-14; page 25, lines 31-page 26, line 13.

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art does not disclose the claimed peptides

As discussed above, neither Middeldorp discloses the claimed peptides.

The prior art does not suggest the claimed invention.

Middeldorp discloses viral peptides, including Epstein Barr nuclear antigen peptides (col. 4, lines 45-53), which are reactive with antibodies to ***anti-EBV*** antibodies (col. 5, lines 1-3; col. 8, lines 32-67) and says that they are useful to make vaccines to prevent infection with EBV and to detect the presence of an EBV infection (col. 8, lines 58-67; col. 9, lines 29-58; col. 10, lines 20-57; col. 11, lines 19-61).

There is no recognition by Middeldorp that EBV peptides may elicit autoantibodies, nor that they are immunoreactive with autoantibodies.

There is no recognition or teaching by Middeldorp that one could, or should, use EBV peptides to induce tolerance in an individual with or at risk of an autoimmune disease.

There is no recognition or teaching by Middeldorp that one could, or should, use the claimed peptide to screen for the likelihood an individual will develop an autoimmune disease.

A prima facie case of obviousness cannot be established by hindsight reconstruction.

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

Middeldorp especially cannot make obvious the methods of use to induce tolerance to an autoantigen, since Middeldorp does not recognize that the EBV proteins may cause autoimmune disease. Middeldorp only discloses methods for vaccinating against EBV using EBV peptides –

i.e., they vaccinate with viral peptides to prevent infection by the virus, not to prevent a disease that develops years after infection with a virus. Only by using hindsight reconstruction could one possibly argue that the claimed method was obvious.

Accordingly, Middeldorp does not make obvious the claimed use of the peptides defined by claim 28.

Rejections under 35 U.S.C. 112, Lack of Enablement

Claims 28 and 29 were rejected under 35 U.S.C. 112, as lacking enablement. This rejection is respectfully traversed.

As the Board of Appeals stated in their decision dated April 25, 2002, in the related case U.S.S.N. 08/475,955, there must be a fact-finding made that supports a finding of non-enablement - mere conjecture is not enough. All the examiner has done here is state that "the field of autoimmunity is unpredictable" and that no evidence has been presented that the claimed method will work. However, there is no legal requirement that applicants do so - the application is presumed to be enabled absent evidence otherwise. The examiner has presented no evidence that applicants' claimed method would not work, only presented situations that suggest there is a possibility some of embodiments might not work or might not work well. As the Board stated in their decision, this is not enough.

The claimed invention is a group of peptides, defined by claims 27 and 29-34, and methods of use, defined by claims 28 and 35-40, based on the discovery that certain epitopes that

are shared with certain viral protein epitopes can elicit an autoimmune disease. The data in the application show the following:

(a) ***Evidence that the claimed peptides induce autoimmune disease***

Serum samples from human patients with lupus all contain autoantibodies immunoreactive with the same octapeptide portions of the Sm autoantigen; of these octapeptides, three are bound by autoantibody present prior to presentation with clinical symptoms. (pages 28-29) Immunization of rabbits with one of these octapeptides causes the rabbits to develop a lupus like disorder, with epitope spreading characteristic of human lupus. (pages 30-31, Figures 5 and 6). Immunization of mice with the octapeptide also causes the mice to develop a lupus like disorder, which is genetically linked. (page 31).

(b) ***Evidence that pediatric patients with autoimmune disease have a statistically significant greater degree of reaction with EBV capsid antigen***

Pediatric patients with Lupus all have antibodies to the Epstein-Barr viral capsid antigen. The difference with normal controls is statistically significant to $p < 0.00000001$. The autoantibodies react with specificity to the virus. The evidence strongly supports the theory that EBV infection is required to develop lupus. (pages 32-46).

(c) ***Lupus patients have elevated levels of autoantibodies to the claimed peptides.***

Lupus patients have elevated levels of antibodies to specific octapeptides (page 46; Figures 3 and 7). The binding patterns are quite distinct when compared to normals without autoimmune disease. (page 47, Table 5, Figures 8D and 8E).

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Additional data was submitted in the Declaration under 37 C.F.R. 1.132 of Dr. John Harley mailed January 6, 1999, following an interview with the examiner.

(a) ***EBV is associated with both Lupus and Inflammatory Polyarthritis***

In response to the examiner's concern that the only disorder tested was lupus, the data in the declaration showed an association between EBV and another autoimmune disorder, inflammatory polyarthritis (pages 1-6).

(b) ***The peptides can be used to induce autoimmunity or tolerance in animal models.***

He also stated that they had been able to administer the peptides shown in the studies described in the application to induce lupus like disease in additional animal studies and to induce tolerance. Rabbits were administered peptide to induce anti-Sm autoimmunity. Based on the schedule of administration, some animals developed the disease and other did not, indicating that they had been tolerized to Sm BB' (page 6-7).

(c) ***There is a genetic component in what animals developed autoimmune disease***

Development of the disease in animal models, as in humans, has a genetic variable. When thirteen different strains of mice were immunized the same way with the same octapeptide, only six strains showed B cell epitope spreading and development of anti-spliceosomal autoimmunity (page 7-8)

(d) ***Certain peptides do not induce autoimmune disease***

The non-antigenic peptides do not induce anti-spliceosomal immunity, indicating that one should be able to use these non-antigenic peptides to interfere with or prevent anti-spliceosomal autoimmunity.

(e) ***Induction of disease is dose-dependent.***

Too high or too low of a dose does not induce disease, consistent with high and low zone tolerance, providing further evidence of tolerance induction (page 8).

(f) ***Induction of disease is dependent on the administration schedule.***

A single immunization of rabbits with the octapeptide induceds tolerance, not B-cell epitope spreading (page 9).

(g) ***The peptide can be chemically modified so there is no autoimmune reaction induced.***

The antigenic octapeptide can be chemically modified so that no anti-spliceosomal autoantibody is detectable in either mice or rabbits immunized with the modified octapeptide (pages 8-9).

(h) ***Peptides from autoantigens can be used to induce autoimmune disease***

A completely different octapeptide derived from the nRNP A protein was used to induce B cell epitope spreading and spliceosomal autoimmunity in rabbits and in mice. A control "non-antigenic" octapeptide derived from the same protein did not induce B cell epitope spreading or spliceosomal autoimmunity in either rabbits or mice (page 9).

In summary, the applicants have shown:

(a) correlation of two totally different autoimmune diseases, systemic lupus erythematosus and inflammatory polyarthritis, with EBV infection, where the disease course is characterized by autoantibody titers highly reactive with specific octapeptides, B-cell epitope spreading and autoimmunity;

(b) induction of B-cell epitope spreading and autoimmunity by immunization of animals using two totally different octapeptides (one from Sm B/B' and one from nRNP A) as antigens;

(c) induction of B-cell epitope spreading and autoimmunity in different animal species: rabbits, mice and baboons;

(d) induction of tolerance by controlling the dose of the octapeptide administered to the animal;

(e) induction of tolerance by controlling the schedule of administration of the octapeptide to the animal;

(f) induction of tolerance by chemical modification of the octapeptide which is used to immunize the animal; and

(g) induction of tolerance by immunization of the animal to a relatively non-antigenic octapeptide.

Applicants also provided literature evidence that shows that *in vitro* binding data of epitopes involved in autoimmune-type diseases are predictive of *in vivo* use. Nicholson, et al., Proc. Natl. Acad. Sci. USA 94(17):9279-9284 (1997) was submitted to show that a slightly

mutated epitope of the proteolipid protein of myelin acts as an antagonist of the T cell receptor and blocks binding of the epitope in vitro and function *in vivo*. Treatment of the peptide halted the destruction of myelin in mice which is caused by an autoimmune attack on the myelin. Gautam, et al., J. Immunol. 161(1):60-64 (1998) showed that the herpesvirus Saimiri contains small epitopes which when injected into a mouse cause experimental autoimmune encephalomyelitis (EAE) indicating that small epitopes can cause disease. Vandenbarke, et al., Immunol. Cell Biol. 76(1):83-90 (1998) showed that vaccinations with epitopes related to EAE and multiple sclerosis caused protective responses to these diseases *in vivo*.

Further evidence showing that methods for inducing tolerance by administration of peptides are known and accepted by those skilled in the art, and that the animal models are predictive of results in humans, was provided with the previously filed appeal brief:

As of 1995, showing use of peptides to induce tolerance was accepted by those skilled in the art: Mor and Cohen "Vaccines to prevent and treat autoimmune diseases" Int. Arch. Allergy Immunol. 108(4):345-349 (1995); Wraith, "Induction of antigen-specific unresponsiveness with synthetic peptides: specific immunotherapy for treatment of allergic and autoimmune conditions" Int. Arch. Allergy Immunol. 108(4):355-359 (1995).

As of 1998, showing that epitope spreading was verifiable by other groups, Singh and Hahn, "Reciprocal T-B determinant spreading develops spontaneously in murine lupus: implications for pathogenesis" Immunol. Rev. 164:201-208 (1998).

As of 2000-2001, theories applicants based methods on are validated and mechanisms beginning to be understood: Wauben, "Immunological mechanisms involved in experimental peptide immunotherapy of T-cell-mediated diseases" Crit. Rev. Immunol. 20(6):451-469 (2000); Harrison and Hafler, "Antigen-specific therapy for autoimmune disease" Curr. Opin. Immunol. 12(6):704-711 (2000); Mocci, et al., "The role of autoantigens in autoimmune disease" curr. Opin. Immunol. 12(6):725-730 (2000); Riemekasten, et al., "Strong acceleration of murine lupus by injection of the SmD1 (83-119) peptide" Arthritis. Rheum. 44(10):2435-2445 (2001).

The data demonstrates the application is fully enabling.

This rejection ignores the evidence of record. First, as noted above, data from more than one peptide has been shown to induce B-cell spreading and development of autoimmunity. Second, this has been demonstrated in mice, rabbits and baboons, which are considered to be appropriate animal models for autoimmunity in humans. Third, the data does show development of tolerance: based on dosage; based on schedule of administration; based on administration of non-antigenic peptide; and based on chemical modification of the antigenic peptide.

Literature has been submitted showing that those skilled in the art believe both that animal models are predictive of efficacy in humans, and that *in vitro* binding data is predictive of *in vivo* activity.

The evidence also makes clear that no undue experimentation is required to induce tolerance, once one is told what peptides to use.

The legal requirements under 35 U.S.C. 112

An invention must have utility. This requirement can be found in U.S.C. § 101 which states," Whoever invents or discovers any new and *useful* process or . . . composition of matter . . . may obtain a patent . . ." (emphasis added). This requirement is also implicitly found in 35 U.S.C. § 112 which requires the specification to provide a written description for "making and *using*" the claimed subject matter.

Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C. § 112, the standard to be applied is the same. *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'f 1987). The *Maas* court stated, "the issue under 35 U.S.C. § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C. § 101 relating to patentable utility." Any analysis of a claim under 35 U.S.C. § 112, first paragraph relating to the use of the claimed subject matter, need only meet the standards of the utility requirement of 35 U.S.C. § 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement of use.

To meet the utility requirement the invention must simply have a "practical utility" in the "real world sense." (*Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA, 1980)). Any use which gives immediate benefit to the public is sufficient to be a "practical utility". *Id.* at 856. It is clear that for an invention to have "practical utility" it must be operative. However, to fail the utility requirement the claimed subject matter must be "totally incapable of achieving a useful result. ("In short, the defense of non-utility cannot be sustained without proof of total incapacity.").) (*Brooktree Corp v.*

Advanced Micro Devices. Inc., 977 F.2d 1555 (Fed. Cir. 1992). See also *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980). An assertion of utility is sufficient to meet the utility requirement unless the assertion is "incredible in the light of the art or factually misleading." (*In re Citron*, 325 F.2d 1389 (CCPA, 1963)).

The standard for utility does not change if the subject matter is pharmaceutical or therapeutic in nature. (*In re Chilowsky*, 229 F.2d 457, 461-2 (CCPA 1956)). "Knowledge of pharmacological activity is an obvious benefit to the public. . . . [A]dequate proof of any such activity constitutes a showing of practical utility" (*Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA, 1980)). The Federal Circuit held that adequate proof of a pharmacological activity can be obtained by merely providing *in vitro* data which are suggestive of an activity *in vivo*. (*Cross v. Iizuka*, 753 F.2d 1040 (CAFC, 1985). "Successful *in vitro* testing . . . [will lead to] . . . *in vivo* testing . . . thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility." *Id.* at 1051. Furthermore, data obtained from animal models clearly is adequate proof. *In re Krimmel* 292 F.2d 948 (CCPA, 1961). The *Krimmel* court stated, "one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant contribution to the art even though it may eventually appear that the compound is without value in the treatment of humans." *Id.* at 953.

Future testing in animals and future testing in humans, even if extensive, does not prevent a specification from meeting the utility requirement. The Court stated in *In re Brana*, "Usefulness in Patent law and in particular in the context of pharmaceutical inventions, necessarily includes the

expectation of further research and development." (*In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995)). If the subject matter covered by pharmaceutical inventions requires future research and development, even after conception and constructive reduction to practice, when then is the utility requirement met? The Federal Circuit has answered this question: "The stage at which an invention in this field becomes useful [i.e. enabled with respect to use requirement] is *well before* it is ready to be administered to humans." (emphasis added) *Id.* at 1568.

The law does not explicitly state what is required to meet the utility requirement for any given pharmacological use because an analysis of utility is a fact based decision. (*Ratheon v. Roper*, 724 F.2d 956). The law is explicitly clear, however, as to what pharmaceutical utility does not require. Pharmaceutical utility does not require human testing (*In re Jolles*, 628 F.2d 1322 (CCPA, 1980); *In re Krimmel*, 292 F.2d 948 (CCPA, 1961); *Cross v. Iizuka*, 753 F.2d 1040 (1985); and *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995)). Pharmaceutical utility does not require animal testing (*In re Krimmel*, 292 F.2d 948 (CCPA, 1961) and *Cross v. Iizuka*, 753 F.2d 1040 (1985)). Pharmaceutical utility does not require a showing of therapeutic safety (*In re Brana* 51 F.3d 1560 (Fed. Cir. 1995) and *In re Irons*, 340 F.2d 974, 978 (CCPA 1965)). Most importantly, pharmaceutical utility does not require a showing of efficacy (See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (1977); I*n re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981)).

Of particular importance is the fact that neither claims 27 and 28 require a specified level of efficacy, nor do they require the cure of any autoimmune disease. The Examiner made it clear in the Office Action dated March 17, 1999, that "No evidence has been set forth which shows the lessening of any symptom of an autoimmune disease by the administration of a composition of the invention." The Examiner also states, "The specification does not set forth any examples wherein the administration of the elected composition in an accepted animal model is able to successfully "alleviate" an already existing autoimmune disease" and "There are no experiments which challenge vaccinated animals with live unattenuated EBV such that the prevention of the autoimmune disease is shown."

However, Applicants are not required to show or provide the types of data that the Examiner demands. The efficacy or the extent of therapeutic effectiveness is to be addressed at the FDA, not the PTO. The Federal Circuit is clear (see above) that the time that pharmaceuticals are ready for patenting is well before they are ready for use or treatment in a human. There is absolutely no requirement one provide animal model data.

Applicants are required to show that the claimed compounds or methods are likely to have the pharmaceutical utility and the Federal Circuit has indicated that *in vitro* data are sufficient for this if it is "suggestive of an activity *in vivo*." (*Cross v. Iizuka*, 753 F.2d 1040 (CAFC, 1985)), and that one skilled in the art could make and use the claimed peptides without undue experimentation.

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g.*, Genentech, Inc. v. Novo Nordisk A/S, 108 F3d at 165, 42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also In re Fisher, 427 F.2d at 839, 166 USPQ at 24; United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (M.I.T. v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement

obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

> The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
>
> Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Id. at § 2164.05 (emphasis added).

With regard to post-filing art, the CAFC stated in In re Brana, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995), that a post-filing date declaration setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. . . . It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed." An important distinction has been made by the Courts between evidence of the knowledge and ability of those of skill in the art at the time of filing and evidence to prove that statements made in the application are correct. In the former case, of course, only evidence which existed prior to the filing of the application, or evidence that certain knowledge existed at the time of filing, is admissible (In re Hogan, 194 USPQ 527 (CCPA 1977)). In the latter case, any evidence, developed at any time, may be submitted for consideration.

The clearest affirmation of the seasonability of factual evidence developed after the filing date of an application is provided by the Court in In re Marzocchi (169 USPQ 367, 370 (CCPA 1971)). In discussing rejections under 35 USC 112 where an examiner asserts that the unpredictability of the art creates a reasonable doubt as to the accuracy of a particular broad statement (in the application) supporting enablement, the Court states:

> Most often, additional factors, such as the teachings of pertinent references[*], will be available to substantiate any doubts that the asserted scope of enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof.

***

Not necessarily *prior* art references, it should be noted, since the question would be regarding the *accuracy* of a statement in the specification, not whether that statement had been made before. [emphasis in the original]

Id. at 367

In *In re Wilson* (135 USPQ 442, 444 (CCPA 1962)), the Court agreed that a reference, published after the filing date of the application, was properly cited to show a state of fact. In *In re Langer* (183 USPQ 288, 297 (CCPA 1974)), the Court again noted that later published references "are properly cited for the purpose of showing a fact." In *In re Rainer* (134 USPQ 343, 345 (CCPA 1962)) the Court found no error in the limited use made of a reference published after Appellant's filing date to show a fact. While all of these cases involved publications cited by the Patent Office in support of rejections, the same standard applies to evidence cited by Appellant. See In re Hogan.

Each piece of post-filing art may be evidence of the enablement of one or more element in the claims. Each piece goes to the issue of enablement of the claimed invention as a whole. The post filing art need only be relevant for the proposition for which it is submitted. It is not necessary, nor is it required, that each element of the claimed invention be within a single post filing art reference. Each fact and piece of evidence supporting enablement can and should be considered for what it shows. It is improper to require one specific form of evidence while

ignoring others. It is the evidence as a whole that must be considered. Elements of the claimed invention *independently* described in the post filing art can cumulatively demonstrate the feasibility of reducing the invention to practice using materials and methods described in the specification and/or known by a skilled artisan as of the time of filing.

Lastly, there is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing* Gould v. Quigg, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.*

The data provided in the application and verified by the experiments described in the Declaration under C.F.R 1.132 by Dr. Harley clearly indicate that the claimed compounds are expected to have an effect on the course of autoimmune diseases. Autoimmune diseases are associated with the production of antibodies to a variety of epitopes and the use of these epitopes for desensitization or the use of vaccines absent the epitopes is clearly indicated by the *in vitro* data linking the autoantibodies of autoimmune diseases and the epitopes of the claimed subject matter. The present application clearly establishes the connection between the epitopes and the autoimmune diseases of the claims.

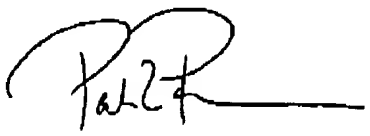
Not withstanding the above Applicants have provided a number of references which indicate that the *in vitro* binding data of epitopes involved in autoimmune-type diseases are predictive of *in vivo* use . See also the abstracts enclosed with the Appeal Brief. These clearly show that those

skilled in the art believe that the results would be predictive of inducing tolerance generally, not just to a specific antigen. Indeed, in view of the abundance of evidence showing that immunization with a single octapeptide induces an immune response to many different epitopes on the protein, unrelated to the immunizing peptide, as a result of B-cell epitope spreading, it would make no sense to limit the claims to inducing tolerance to a particular epitope.

Summary

Based on the foregoing, the claimed compositions and methods are both enabled and have utility. The claimed compositions and methods are neither disclosed by nor obvious from the prior art cited by the examiner. Allowance of all of claims 27-40 as amended is earnestly solicited.

Respectfully submitted,



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